Maintenance olaparib (Lynparza®) for the treatment of patients with germline BRCA-mutated metastatic pancreatic cancer

General information [1, 2]

Drug description	Indication
Olaparib is a poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor	Lynparza® is indicated as monotherapy for the maintenance treatment of adult patients with germline BRCA1/2-mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen.

Current treatment [3]

- According to NICE guidance, patients with metastatic pancreatic cancer should be offered:
  - A combination of folic acid, fluorouracil, irinotecan and oxaliplatin (FOLFIRINOX) as a first-line treatment
  - Gemcitabine should be offered to patients who are not well enough to tolerate FOLFIRINOX
  - Oxaliplatin-based chemotherapy as second-line treatment should be considered for people who have not had first-line oxaliplatin
  - Gemcitabine-based chemotherapy as second-line treatment should be considered for people whose cancer has progressed after first-line FOLFIRINOX
  - Surveillance should be offered for pancreatic cancer with BRCA mutations.

Regulatory status

EMA [1]

Approval status for this indication: On 28 May 2020, the CHMP adopted a new indication in adenocarcinoma of the pancreas.

Other indications:

- Ovarian cancer: Lynparza® is indicated as monotherapy for the:
  - maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy
  - maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy
- Breast cancer
  - Lynparza® is indicated as monotherapy for the treatment of adult patients with germline *BRCA1/2*-mutations, who have HER2 negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments
  - Patients with hormone receptor-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy.

FDA [4]

Approval status for this indication: On 27 December 2019, the FDA approved Lynparza® for the maintenance treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) metastatic pancreatic adenocarcinoma, as detected by an FDA-approved test, whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.

Other indications: Lynparza® is indicated in:

- Ovarian cancer:
  - for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy.
  - in combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with HRD-positive status defined by either:
    - a deleterious or suspected deleterious BRCA mutation, and/or
    - genomic instability
  - for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy
  - for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy
- Breast cancer:
  - for the treatment of adult patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy.
- Prostate cancer:
  - for the treatment of adult patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone.

Posology [5]

- Patients should start treatment with olaparib no later than 8 weeks after completion of their final dose of the platinum-containing regimen.
- It is recommended that treatment be continued until progression of the underlying disease or unacceptable toxicity
- Important differences in posology between olaparib capsules and tablets: Lynparza® capsules (50 mg) should not be substituted for Lynparza® tablets (100 mg and 150 mg) on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation.

Costs

112 Lynparza® tablets 150 mg = **€ 5,059.29** (ex-factory price) [6]
POLO trial patients received maintenance olaparib tablets at a dose of 300 mg daily → approx. € 2,530 for 28 days of olaparib treatment.
Among patients of the POLO trial, the median duration of treatment was 6.0 months → costs of approx. € 15,174.87

Study characteristics [2, 7]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
POLO NCT02184195	154	Maintenance olaparib tablets 300 mg twice daily	Placebo	PFS	randomized, double-blind, placebo-controlled, phase 3, ongoing[1]	-	AstraZeneca and others	Link

Efficacy (I vs. C)

Median PFS: 7.4 months vs. 3.8 months; HR for disease progression or death, 0.53; 95% CI, 0.35 to 0.82; p=0.004)
Median OS (interim analysis at a data maturity of 46%): 18.9 vs. 18.1 months, HR 0.91; 95% CI, 0.56 to 1.46; p=0.68)
Second PFS[2] (at a data maturity of 46%, median): 13.2 vs. 9.2 months, HR 0.76; 95% CI, 0.46 to 1.23
Response rate (among patients with measurable disease at baseline): 23% vs. 12% (odds ratio, 2.30; 95% CI, 0.89 to 6.76).
Median duration of response: 24.9 (95% CI, 14.8 to could not be calculated) vs. 3.7 months (95% CI, 2.1 to could not be calculated)
Median time to response: 5.4 vs. 3.6 months
HRQoL: no significant between-group difference (−2.47 points; 95% CI, −7.27 to 2.33)

Safety (I vs. C)

Any AE grade ≥3: n=36/91 (40%) vs. n=14/60 (23%)
SAEs: 24% vs. 15%
Death[3]: No AEs that occurred during the trial intervention resulted in death
Discontinuation[4]: n=5/91 (5%) vs. n=1/60 (2%)

ESMO-MCBS version 1.1

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2b	≤6 months	+3.6 months	0.53 (0.35-0.82)	HR ≤0.65 AND gain ≥1.5 months	3	-	ND	-	3
Adapted	NC	2b	≤6 months	+3.6 months	0.53 (0.35-0.82)	HR ≤0.65 AND gain ≥1.5 months	3	+17% grade ≥3 AEs, +3% discontinuation	-	-1	2

Risk of bias (study level)

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	yes	yes	unclear[5]	yes[6]	unclear

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Abbreviations: AE=adverse event, AJ=adjustment, BRCA1=Breast Cancer susceptibility gene, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FIGO= The International Federation of Gynecology and Obstetrics, FM=final magnitude of clinical benefit grade, HR=hazard ratio, HRD= homologous recombination deficiency, HRQoL=health-related quality of life, HRR= homologous recombination repair, MG=median gain, n=number, ND=no difference, SAE=serious adverse event, ST=standard treatment, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life

[1] POLO trial is ongoing until 02/2021
[2] Time from randomization to second disease progression or death
[3] Death due to AE(s)
[4] Discontinuation due to AE(s)
[5] Trial is ongoing
[6] Industry-funded; The trial was designed by the first and last authors in collaboration with the sponsor. The sponsor was responsible for overseeing the collection, analysis, and interpretation of the data. The co-developer of olaparib provided input regarding the interpretation of the data.

References:

1. European Medicines Agency (EMA). Medicines. Lynparza. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/lynparza.
2. Golan T, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall MJ, et al. Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer N Engl J Med 2019; 381:317-327 [Available from: https://www.nejm.org/doi/10.1056/NEJMoa1903387.
3. National Institute for Health Research. Olaparib for metastatic pancreatic cancer with gBRCA mutation [Available from: http://www.io.nihr.ac.uk/wp-content/uploads/2018/08/11186-Olaparib-for-pancreatic-cancer-V1.0-JUL2018-NON-CONF.pdf.
4. U.S. Food and Drug Administration (FDA). Development & Approval Process | Drugs. Drug Approvals and Databases. Resources for Information | Approved Drugs . FDA approves olaparib for gBRCAm metastatic pancreatic adenocarcinoma [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-olaparib-gbrcam-metastatic-pancreatic-adenocarcinoma.
5. European Medicines Agency (EMA). Lynparza: EPAR - Product Information [Available from: https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_en.pdf.
6. Österreichischer Apother-Verlag. Warenverzeichnis online. [Available from: https://warenverzeichnis.apoverlag.at/.
7. U.S. National Library of Medicine. ClinicalTrials.gov [Available from: https://clinicaltrials.gov/ct2/show/NCT02184195.